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(54) Title: A PHARMACEUTICAL COMPOSITION FOR TREATING DYSMENORRHEA AND PREMATURE LABOR		
(57) Abstract The present invention teaches a composition comprising a β -adrenergic agonist in a bioadhesive carrier. Preferably, the composition comprises terbutaline in polycarbophil. The present invention additionally teaches the local administration of a β -adrenergic agonist for the purpose of treating or preventing dysmenorrhea or premature labor. Using this composition and the method of treatment provides sufficient local levels of the drug to provide therapeutic efficacy, but avoids many untoward adverse events.		

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A PHARMACEUTICAL COMPOSITION FOR TREATING DYSMENORRHEA AND PREMATURE LABOR

This application claims the benefit of United States Provisional Application No. 60/058,789, filed September 12, 1997, which is incorporated herein by reference.

Field of the Invention

5 The invention relates to a pharmaceutical composition and the local administration thereof for the purpose of treating or preventing dysmenorrhea or premature labor.

Background of the Invention

10 Both dysmenorrhea and premature labor affect significant numbers of American women; however, treatment regimens are still lacking for both conditions. Dysmenorrhea, menstrual cramps, affects on average over 50% of women and results in frequent absenteeism or loss of activity. *Andersch, B., Milsom I., An Epidemiologic study of young women with dysmenorrhea, A.J.O.G., 144:655-60 (1982).* Young women report a somewhat higher incidence of
15 dysmenorrhea than the average, with estimates ranging from 67% to 72%. *Harlow, S.D., Parck M., A longitudinal study of risk factors for the occurrence, duration and severity of menstrual cramps in a cohort of college women, Br. J. Obstet. Gynaecol., 103:1134-42 (1996).* Severe pain has been reported by 7 to 15% of women. *Id.*

20 In the United States alone an estimated 140 million work and school hours are lost per year due to this condition. *Klein, J.R., Litt, I.F., Epidemiology of adolescent dysmenorrhea, Pediatrics, 68:6661-64 (1981).* About 42% of United States university students between the ages of 17 and 19 have had to be absent from their daily activities at least once due to dysmenorrhea. *Id.* Approximately
25 15% of young women have one to three days of incapacitation each month and dysmenorrhea is the leading cause of short-term school absenteeism among adolescent young women. *Id.* This disease, with its constant regularity, results in notable social, educational, and economic losses in this country.

30 Dysmenorrhea consists of painful uterine cramping and is often accompanied by associated symptoms including nausea, vomiting, diarrhea, and

lower backaches. Treatments for dysmenorrhea currently focus on the use of non-steroidal antiinflammatory drugs (NSAIDs). These drugs include, for instance, naproxen, ibuprofen, mefenamic acid, and meclofenamate sodium. Oral contraceptives are also used by some women in the treatment of dysmenorrhea.

5 Despite the fact that these two regimens can be used together, the recurring problems of dysmenorrhea have not been eliminated for many women.

Specifically, the painful uterine cramping associated with dysmenorrhea is probably triggered by vasopressin and increased production of prostaglandins. The current method of treatment, with NSAIDs, blocks prostaglandin production and acts as a painkiller. Although this method of treatment is effective in some women and decreases symptoms in other women, researchers have wondered whether blocking the dysmenorrheic process at an earlier step would provide more effective treatment in the prevention of uterine cramping.

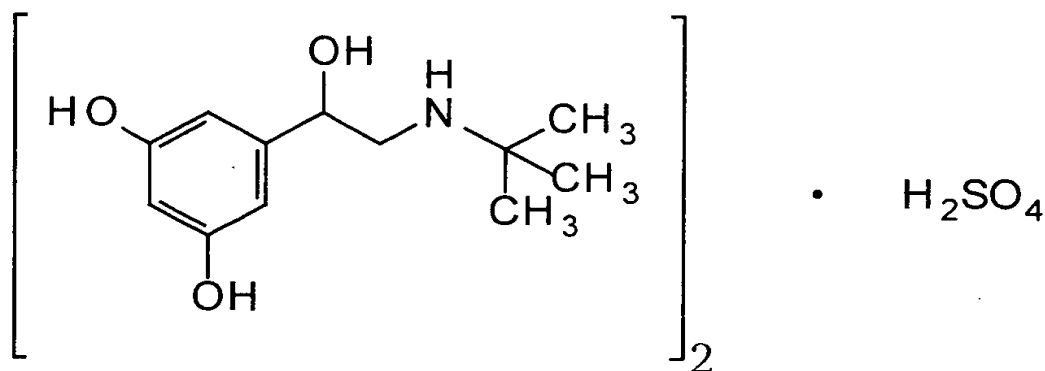
10 Although no link has formally been established, some researchers believe that untreated dysmenorrhea may play a role in the genesis of such serious clinical conditions as endometriosis. Recent studies have shown that endometriosis is associated with dyskinetic patterns of uterine contractions at the time of menses. *Salamanca, A., Beltran, E., Subendometrial Contractility in Menstrual Phase Visualized by Transvaginal Sonography in Patients with Endometriosis. Fertil. Steril., 65:193-95 (1995).* Additionally, the symptoms of dysmenorrhea can often mask the more serious disease of endometriosis. Symptoms of dysmenorrhea often occur in women with endometriosis for nearly ten years on average prior to laproscopic diagnosis of the later disease. *Hadfield, R., Mardon, H., Barlow, D., Kennedy, S., Delay in the Diagnosis of Endometriosis: A Survey of Women from the U.S.A. and U.K. Human Reprod., 11:878-80 (1996).*

25 Premature labor also affects a significant number of women in the United States. Preterm delivery is defined as delivery prior to 30 weeks of gestation. This phenomenon complicates 8 to 10% of births in the United States and is a leading cause of neonatal morbidity and mortality. *Lockwood, C.J., The diagnosis of PTL and the prediction of preterm delivery, Clinical Obstetrics and Gynecology, Pitkin, R.M., Scott, J.R. (eds.), 38:675-678 (1995).* In fact, 30 prematurity causes 75% of perinatal deaths in this country. *McCombs, J., Update*

on Tocolytic Therapy, *Annals of Pharmacotherapy*, 29:515-522 (1995). Premature infants also have an increased risk of other serious conditions, including respiratory distress syndrome, hyaline membrane disease, intracranial intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and have an increased incidence of cerebral palsy. *Id.*

Currently, preventing preterm delivery focuses on the early diagnosis of impending premature labor in women with intact membranes. Oral tocolytic agents, or uterine relaxants, are the treatment of choice. Tocolytic agents include progestational compounds, β -adrenergic agonists, NSAIDs, calcium agonists, oxytocin, or vasopressin agonists, and potassium channel openers. The most widely used of these are the β -adrenergic agonists such as terbutaline and ritodrine. It should be noted, however, that of the β -adrenergic agonists, only ritodrine is approved by the F.D.A. for use in preterm labor. Other β -adrenergic agonists, such as terbutaline, are approved for other conditions (e.g., asthma) but have been used by practitioners in the treatment of premature labor. As these drugs are given orally, however, treatment is accompanied by serious side effects. Research has failed to produce a β -adrenergic agonist that is selective for the receptors in the uterus and consequently lacking of some of the most serious adverse events.

Terbutaline is a β -adrenergic agonist. Its chemical formula is 5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-1,3-benzenediol. The empirical formula of terbutaline is $C_{12}H_{19}NO_3$. Its molecular weight is 225.29. Its structural formula is as follows:



Terbutaline, as a β -adrenergic agonist, has been used primarily as a bronchodilator.

β -adrenergic agonists exert their pharmacologic effects by activation of adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Activation of adenylyl cyclase by β -adrenergic agonists increases intracellular levels of cAMP. Cyclic AMP in turn reduces the availability of intracellular free Ca^{2+} , which is required for the activation of myosin light-chain kinase, the enzyme that phosphorylates myosin and thereby allows it to combine with actin to form actomyosin. Lack of Ca^{2+} results in disruption of the actin-myosin interaction, with resultant inhibition of smooth muscle contractility. Due to their direct effects on smooth muscle contractility, β -adrenergic agonists, such as terbutaline, may prove to be an effective therapy for both dysmenorrhea and premature labor.

In fact, oral and intravenous terbutaline has been used as a reasonably effective therapy for preterm labor. Studies have shown that oral or IV therapy can stop contractions or postpone delivery. Lyrenas, S., Grahnen, A., Lindberg, B., et. al., *Pharmacokinetics of Terbutaline During Pregnancy*, *Eur. J. Clin. Pharmacol.*, 29:619-623 (1986); Berg, G., Lindberg, C., Ryden G., *Terbutaline in the Treatment of Preterm Labour*, *Eur. J. Respir. Dis.*, 65:219-230 (1984).

Adverse events can present significant problems in the treatment of preterm labor with terbutaline and are discussed further below.

A few studies also document the use of terbutaline in the treatment of dysmenorrhea. In one study, treatment with IV terbutaline inhibited myometrial activity, increased blood flow to the uterus, and relieved the pain occurring during uterine contractions accompanying dysmenorrhea. Åkerlund, M., Andersson, K.E., and Ingemarsson, E., *Effects of Terbutaline on Myometrial Activity, Uterine Blood Flow, and Lower Abdominal Pain in Women with Primary Dysmenorrhoea*, *Br. J. of Obstet. & Gyn.*, 83(9):673-78 (1976). Terbutaline inhalers have even been evaluated for the treatment of dysmenorrhea. Kullander, S., Svanberg, L., *Terbutaline Inhalation for Alleviation of Severe Pain in Essential Dysmenorrhea*, *Acta Obstet. Gynecol. Scand.*, 60:425-27 (1981). This therapy did provide some efficacy; however, treatment was not sufficient for most patients, who had to

supplement with other medications for adequate relief. Further, the effect of each spray lasted as little as 1 hour. *Id.* One other β -adrenergic agonist, salambutol, showed pain relief when administered intravenously. *Lalos, O., Joelsson, I., Effect of Salbutamol on the Non-Pregnant Human Uterus In Vivo, Acta Obstet. Gynecol. Scand., 60:349-52 (1981).*

Several problems with administration and adverse effects, however, prevent women affected by dysmenorrhea and premature labor from being able to take full advantage of this therapy. First, β -adrenergic agonists such as terbutaline have a low bioavailability after oral administration. These pharmaceuticals are well absorbed but have extensive first-pass sulphation. Bioavailability has been estimated at between 15 and 20%. Concomitant food intake additionally decreases bioavailability by a further 30%. *Bricanyl: Scientific brochure, Astra France Laboratories (1993).*

Second, adverse effects significantly limit the current utility of terbutaline in the treatment of preterm labor and dysmenorrhea. Placental transfer of β -adrenergic agonists such as terbutaline is relatively rapid; thus, adverse effects are observed in the fetus and neonate while treating premature labor using oral administration. *Morgan, D.J., Clinical Pharmacokinetics of β -Agonists, Clin. Pharmacokin., 18:270-294 (1990).* Thus, when treating preterm labor, adverse events can affect not only the woman but also her child.

The most serious adverse events are cardiovascular in nature. Intravenous administration of terbutaline has been associated with palpitations and peripheral tremors. *Åkerlund, M., Andersson, K.F., Ingemarsson, I., Effects of Terbutaline on Myometrial Activity, Uterine Blood Flow and Lower Abdominal Pain in Women With Primary Dysmenorrhea. Br. J. Obstet. Gynecol., 83:673-78 (1976).* As a sympathomimetic amine, terbutaline can cause problems in patients with cardiovascular disorders (including arrhythmia, coronary insufficiency and hypertension), as well as with patients with hyperthyroidism, diabetes mellitus, or a history of seizures. Significant adverse reactions have been reported following administration of terbutaline to women in labor including pulmonary edema and hypoglycemia in the mother and or neonate child. Intravenous terbutaline has also been reported to aggravate preexisting diabetes and ketoacidosis. Other

adverse events include: tremors, nervousness, increased heart rate, palpitations, and dizziness. Less frequent adverse effects include headaches, drowsiness, vomiting, nausea, sweating, muscle cramps, and ECG changes.

These adverse effects have precluded the use of β -agonists such as
5 terbutaline to prevent or treat dysmenorrhea as it considered to be a benign or non-threatening condition. *Åkerlund, M., Andersson, K.E., and Ingemarsson, E., Effects of Terbutaline on Myometrial Activity, Uterine Blood Flow, and Lower Abdominal Pain in Women with Primary Dysmenorrhoea, Br. J. of Obstet. & Gyn., 83(9):673-78 (1976).* Further, the risks involved have limited the use of these
10 pharmaceutical agents in the treatment of preterm delivery and premature labor as the benefits must be balanced carefully against the seriousness of the adverse events involved.

In an attempt to address the severity of the adverse events involved, researchers have been attempting to identify another effective means for
15 administering the drug that would decrease the risk involved. It is known that terbutaline can be administered directly to the uterus, resulting in preferential local concentrations as compared to peripheral circulation concentrations. *Kullander et al.* studied the correlation between the uterine and blood concentrations of terbutaline after insertion of a terbutaline-impregnated polymer ring (10%
20 terbutaline sulfate in a 5 g vaginal ring), terbutaline in a cellulose gel (0.1 mg in 1 mL cellulose gel), or a placebo ring in a patient 24 hours before hysterectomy. *Kullander, S., Svanberg, L., On resorption and the effect of vaginally administered terbutaline in women with premature labor. Acta. Obstet. Gynecol. Scand., 64:613-16 (1985).* The methods followed in this reference, however, have distinct
25 disadvantages. The water soluble cellulose-gel used can wash away and the use of a polymer ring can be uncomfortable and unpalatable for the woman, and thus both are distinctly disadvantageous.

Other pharmaceutical compounds with problematic adverse events have been successfully administered locally. The bioadhesive carrier of the present
30 invention has been used in other drug delivery systems, although with different results than in the present invention. For example, polycarbophil is a main ingredient in the vaginal moisturizer Replens®. It has also been used as a base

for compositions with other active substances such as progesterone (Crinone®) (see U.S. Pat. No. 5,543,150) and Nonoxynol-9 (Advantage-S) (see U.S. Pat. No. 5,667,492).

5 Additionally, it is important that pharmaceutical compositions do not interfere with all contractions and the homeostasis of menstruation. As menstrual blood does not clot, normal, regularized contractions are helpful to stop the bleeding. If there are no contractions, then the patient may not stop bleeding and may hemorrhage. Thus, it is an object of the invention to interfere with the dyskinetic contractions causing dysmenorrhea, without stopping contractions
10 entirely.

Summary of the Invention

The present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a β -adrenergic agonist together with a pharmaceutically acceptable bioadhesive carrier and the local
15 administration of a β -adrenergic agonist for the purpose of treating or preventing dysmenorrhea or premature labor. Using this composition and the method of treatment provides sufficient local levels of the drug to provide therapeutic efficacy, but avoids many untoward adverse events.

Brief Description of the Drawings

20 FIG. 1 illustrates the serum terbutaline levels in a single dose study. Doses were 4 mg, 2 mg, and 1 mg. The terbutaline gel was administered transvaginally once.

FIG. 2 illustrates the serum terbutaline levels in a multiple dose study. Doses were 4 mg, 2 mg, and 1 mg. The terbutaline gel was administered
25 transvaginally once daily for six days.

FIG. 3 illustrates the serum terbutaline levels in a single dose study. The dose given was 8 mg. The terbutaline gel was administered transvaginally once.

FIG. 4 illustrates the serum terbutaline levels in a multiple dose study. The dose given was 8 mg. The terbutaline gel was administered transvaginally
30 once daily for six days.

FIG. 5 illustrates mean heart rates in a single dose study. Doses were 8 mg, 4 mg, 2 mg, and 1 mg. The terbutaline gel was administered transvaginally once.

5 FIG. 6 illustrates mean heart rates in a multiple dose study. Doses were 8 mg, 4 mg, 2 mg, and 1 mg. The terbutaline gel was administered transvaginally once daily for six days.

FIG. 7 illustrates the myometrial terbutaline influx in an *ex vivo* uterine perfusion model.

Detailed Description Of the Invention

10 The present invention is related to a composition comprising therapeutically effective amount of a β -adrenergic agonist together with a pharmaceutically acceptable bioadhesive carrier. Preferably terbutaline is used as the β -adrenergic agonist. The present invention preferably comprises a β_2 specific adrenergic agonist. Other acceptable β -adrenergic agonists include ritodrine,
15 isoxsuprine, fenoterol, salambutol, hexoprenaline, metaproterenol, bitolterol and pirbuterol. The invention comprises a uterine smooth muscle relaxant for both pregnant and non-pregnant women and has been specifically designed for vaginal administration. The bioadhesive carrier, which may be in a gel formulation, contains a polycarbophil base designed to give controlled and prolonged release
20 of terbutaline, or another β -adrenergic agonist, through the vaginal mucosa. This route of administration avoids first-pass metabolism problems. The direct delivery to the uterus allows for lower systemic drug concentrations. These two properties help avoid many significant adverse events.

25 The present invention is additionally related to a method of preventing or treating dysmenorrhea comprising administering the composition vaginally. Additionally, the present invention includes a method of preventing or treating premature labor comprising administering the composition vaginally. Most preferably, in preventing or treating both conditions, 1 to 1.5 g of the composition is administered; although, acceptable amounts of the composition to be
30 administered include 0.5 to 2.5 g. The composition administered can contain between 1 to less than about 8 mg of terbutaline per dose, preferably containing 1 to 4 mg, and most preferably containing 2 to 4 mg. Dosages of 8 or more mg are

not recommended, however, because side effects may be noted in some individuals at such levels. The composition can be administered every 12 to 48 hours, but is preferably administered every 24 hours. The composition can be administered during dysmenorrhea or optionally including one or more days prior to the anticipated onset of dysmenorrhea. Similarly, the composition may be administered during premature labor or to prevent the onset of anticipated premature labor.

The present invention comprises a dosing regimen and manner of treating dysmenorrhea. In practicing the invention, a patient need not wait until the onset of menses and the occurrence of pain to begin treatment. The present invention comprises administration of the composition as soon as the patient realizes that she is nearing the onset of menses, for example within a day or two. This method of administration is based on pharmacokinetic data below, and prevents the process of dyskinetic contractions from occurring, rather than treating them once the contractions have already begun.

Another important aspect of the invention is that the uterorelaxant formulation can correct dysmenorrhea and its dyskinetic contractions, without interfering with the normal contractions and bleeding during menstruation. Dysmenorrhea appears to involve dyskinetic contractions, which are erratic and abnormal. This is in contrast to other theories of dysmenorrhea as comprises solely an increase in the amplitude and frequency of contraction. The inventors believe that in dysmenorrhea the nature of contractions change so that there are not only antegrade contractions (fundus to cervix), but also retrograde contractions (cervix to fundus), and non-functional fibrillations. The composition of the present invention appears to provide relief by way of a selective action on the dyskinetic contractions without preventing the normal, regularized contractions necessary for menstruation.

The specific drug delivery formulation chosen and used in the examples below comprises a cross-linked polycarboxylic acid polymer formulation, generally described in U.S. Patent No. 4,615,697 to Robinson (hereinafter "the '697 patent"), which is incorporated herein by reference. In general, at least about eighty percent of the monomers of the polymer in such a formulation should

contain at least one carboxyl functionality. The cross-linking agent should be present at such an amount as to provide enough bioadhesion to allow the system to remain attached to the target epithelial surfaces for a sufficient time to allow the desired dosing to take place.

5 For vaginal administration, such as in the examples below, preferably the formulation remains attached to the epithelial surfaces for a period of at least about twenty-four to forty-eight hours. Such results may be measured clinically over various periods of time, by testing samples from the vagina for pH reduction due to the continued presence of the polymer. This preferred level of bioadhesion
10 is usually attained when the cross-linking agent is present at about 0.1 to 6.0 weight percent of the polymer, with about 1.0 to 2.0 weight percent being most preferred, as long as the appropriate level of bioadhesion results. Bioadhesion can also be measured by commercially available surface tensiometers utilized to measure adhesive strength.

15 The polymer formulation can be adjusted to control the release rate of the β -adrenergic agonist, such as terbutaline, by varying the amount of cross-linking agent in the polymer. Suitable cross-linking agents include divinyl glycol, divinylbenzene, N,N-diallylacrylamide, 3,4-dihydroxy-1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene and similar agents.

20 A preferred polymer for use in such a formulation is Polycarbophil, U.S.P., which is commercially available from B.F. Goodrich Speciality Polymers of Cleveland, OH under the trade name NOVEON®-AA1. The United States Pharmacopeia, 1995 edition, United States Pharmacopeial Convention, Inc., Rockville, Maryland, at pages 1240-41, indicates that polycarbophil is a polyacrylic
25 acid, cross-linked with divinyl glycol.

Other useful bioadhesive polymers that may be used in such a drug delivery system formulation are mentioned in the '697 patent. For example, these include polyacrylic acid polymers cross-linked with, for example, 3,4-dihydroxy-1,5-hexadiene, and polymethacrylic acid polymers cross-linked with, for example,
30 divinyl benzene.

Typically, these polymers would not be used in their salt form, because this would decrease their bioadhesive capability. Such bioadhesive polymers may

be prepared by conventional free radical polymerization techniques utilizing initiators such as benzoyl peroxide, azobisisobutyronitrile, and the like. Exemplary preparations of useful bioadhesives are provided in the '697 patent.

5 The bioadhesive formulation may be in the form of a gel, cream, tablet, pill, capsule, suppository, film, or any other pharmaceutically acceptable form that adheres to the mucosa and does not wash away easily. Different formulations are further described in the '697 Patent, which is incorporated herein by reference.

10 Additionally, the additives taught in the '697 patent may be mixed in with the cross-linked polymer in the formulation for maximum or desired efficacy of the delivery system or for the comfort of the patient. Such additives include, for example, lubricants, plasticizing agents, preservatives, gel formers, tablet formers, pill formers, suppository formers, film formers, cream formers, disintegrating agents, coatings, binders, vehicles, coloring agents, taste and/or odor controlling agents, humectants, viscosity controlling agents, pH-adjusting agents, and similar agents.

15 The specific preparation (COL-2301) used in the studies discussed in the examples consists of the following ingredients.

Table 1: Preferred Compositions

Active Ingredient mg/g	1.0	2.0	4.0
Terbutaline (sulfate) % (w/w)	0.1%	0.2%	0.4%
Purified Water	755.4	754.4	752.4
Glycerin	139.0	139.0	139.0
Light liquid paraffin	42.0	42.0	42.0
Carbomer 934P	30.0	30.0	30.0
Polycarbophil	20.0	20.0	20.0
Methylparaben	1.8	1.8	1.8
Sorbic acid	0.8	0.8	0.8
Sodium Hydroxide	0.0-2.0	0.0-2.0	0.0-2.0
LABRAFIL® M2130	10	10	10

Sorbic acid is a preservative, which may be substituted by any other approved preservative, such as benzoic acid or propionic acid.

Carbomer is a gel former, preferably Carbopol 934P, but may be substituted by other gel formers including, but not limited to, Carbomer 974P, Carbomer 980, methyl cellulose or propyl cellulose.

LABRAFIL® M2130 is a lubricant/whitening agent to provide lubricity and add color to the gel; alternatives may be used, and coloring may be left out altogether.

Glycerin is a humectant; alternative humectants include, for example, propylene glycol or dipropylene glycol.

Preparation of the formulation involves hydration of the polymers, separate mixing of water-soluble ingredients (the "polymer phase") and oil-soluble ingredients (the "oil phase"), heating and mixing of the two phases, and homogenization of the mixture. All ingredients in COL-2301 are well known and readily available from suppliers known in the industry.

The polymer phase may generally be prepared by mixing the water (with about 3% excess volume of water to account for evaporative losses), sorbic acid, and methylparaben together. This mixture is heated to 75°C. The solution is

cooled, generally to room temperature, and then the polycarbophil and Carbomer are added. The polymers are hydrated by mixing for several hours, generally about 2-3 hours until a uniform, smooth, homogenous, lump-free gel-like polymer mixture is obtained. When the polymers are completely hydrated, the terbutaline is added and mixed in, until a homogeneous suspension is obtained.

The oil phase is generally prepared by melting together the LABRAFIL® M2130, glycerin, and light liquid paraffin, by heating to 75 to 78°C. The mixture is cooled to about 60°C., while the polymer phase is warmed to about the same temperature. The polymer phase is then added to the heated oil phase. The two phases are mixed thoroughly, producing a uniform, creamy white product. Sodium hydroxide is added, as needed, to produce a pH of about 2.5-4.5, generally about 4. When the mixture has cooled, it is de-aerated.

As will be apparent to those skilled in the art, the composition of the formulation can be varied to affect certain properties of the formulation. For example, the concentration of the bioadhesive polymer can be adjusted to provide greater or lesser bioadhesion. The viscosity can be varied by varying the pH or by changing the concentration of the polymer or gel former. The relative concentrations of the oils compared to the water can be varied to modulate the release rate of the terbutaline from the drug delivery system. The pH can also be varied as appropriate or to affect the release rate or bioadhesiveness of the formulation.

One of the surprising, but important aspects of the present formulation is that it allows the drug to be administered effectively even during menses. The particular bioadhesive qualities prevent the composition from being diluted or washed away, as would be expected with other bioadhesive preparations. This characteristic increases the utility of the present formulation.

Additionally, in light of the information disclosed in U.S. Pat. No. 5,543,150, it now appears that this bioadhesive formulation can provide local vaginal administration of different drugs to yield significant local drug levels while maintaining serum levels low enough to avoid most undesired side effects. It was a surprising result that this formulation serves as an acceptable carrier for two different active ingredients -- progesterone, and now terbutaline. Now, given its

demonstrated flexibility and range of efficacy, it is reasonable to expect that the bioadhesive formulation will work with other active ingredients as well.

EXAMPLES

Example 1: The Pharmacokinetic Parameters of the Terbutaline

Composition,

A Single Dose Study

The objective of this study was to assess the pharmacokinetic parameters of the terbutaline and polycarbophil composition following a single dose regimen comparing progressively increasing concentrations. This open-label study was conducted in ten healthy female volunteers with a mean age of $25 \pm \text{SD}$ (Standard Deviation) of 3.93 years. This study consisted of a 30 day screening period and a 24 hour treatment period with a follow-up evaluation conducted two days after administration of the final dose. The drug was administered transvaginally at 9:00 a.m. A wash out period of at least one week as observed between each of the four doses of the drug. All subjects were given an

estrogen-progestative pill, to ensure that all study participants were at the same point in their menstrual cycle. They began dosing on day 7 to 10 of their pill intake for the single dose study. Serum terbutaline concentrations were obtained from blood samples collected predosing on the mornings of treatment, at frequent intervals during the initial 24 hours post dose (0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 hours) and at 48 hours post dose. Serum terbutaline concentrations were determined using gas chromatography-mass spectrometry. Pharmacokinetic parameters were computed using concentration-time data for each subject following intake of the last dose of investigational drug on the morning of study day 6. The following pharmacokinetic parameters were computed: area under the drug concentration-time curve from time 0 to time t (AUC_{0-t}), where t is the time of the last measurable concentration; peak drug concentration (C_{max}); time to peak drug concentration (t_{max}); steady state drug concentration (C_{ss}); and, elimination half-life ($t_{1/2}$).

All ten subjects completed the study for the 0.1%, 0.2%, and 0.4% (w/w) concentrations. For each dose, the onset of serum terbutaline concentrations occurred within 1 to 2 hours. (See Figure 1 and Table 2 showing terbutaline

concentrations for each tested dose). Terbutaline concentrations increased slowly reaching C_{\max} after 13-14 hours and thereafter remained flat (steady state) for 24 hours with a mean steady state concentration (C_{ss}) of approximately 300 pg/mL with the 0.4% concentration. Concentrations were still detectable for up to 48 hours (mean \pm SEM (Standard Error of the Mean) of 113.11 ± 32.25 pg/mL for the 0.4% concentration). Terbutaline absorption exhibited dose-dependent pharmacokinetics as reflected by the increase in AUC_{0-48} values (see Table 2 and Figure 1) to increases in terbutaline dosing. Mean $t_{1/2}$ estimates varied from 18 to 29 hours according to the dose administered and markedly exceeded measured $t_{1/2}$ after terbutaline administration by intravenous or subcutaneous routes, as had been found in the prior art.

TABLE 2: Single Dose Study, Pharmacokinetic Parameters

Single Dose Study		Pharmacokinetic Parameters (mean \pm SEM)				
Terbutaline Dose	n	C_{\max} (pg/mL)	T_{\max} (h)	C_{ss} (pg/mL)	$t_{1/2}$ (h)	$AUC_{0 \text{ to } 48}$ (pg.h/mL))
0.1%	10	117 ± 59	13 ± 6	56 ± 41	18 ± 12	2281 ± 1836
0.2%	10	297 ± 170	13 ± 6	191 ± 108	29 ± 15	8011 ± 4699
0.4%	10	479 ± 149	14 ± 7	294 ± 115	24 ± 16	11893 ± 5277

**Example 2: The Pharmacokinetic Parameters of the Terbutaline Composition,
A Multiple Dose Study**

The multiple dose study was an open-label study conducted in 12 healthy female volunteers with a mean age \pm SD of 25 ± 4.13 years. The dose used in this study was 0.4%. This study consisted of a 30 day screening period, a 6 day treatment period, and a 2 day follow-up. The drug was administered transvaginally once daily at 9:00 a.m. All subjects were given an

estrogen-progestative pill, to ensure that all study participants were at the same place in their menstrual cycle. They began dosing on day 13 to 16 of their pill intake for the multiple dose study. Serum terbutaline concentrations were obtained from blood samples collected predosing on the mornings of treatment, at frequent intervals during the initial 24 hours post-dose (0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours), and at 48 hours post-dose. Samples were also obtained just before each administration and at regular intervals after the last dose (0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours). Serum terbutaline concentrations were determined using gas chromatography-mass spectrometry.

Pharmacokinetic parameters were computed using concentration-time data for each subject following intake of the last dose of investigational drug on the morning of study day 6. The following pharmacokinetic parameters were computed: area under the drug concentration-time curve from time 0 to time t (AUC_{0-t}), where t is the time of the last measurable concentration; peak drug concentration (C_{max}); time to peak drug concentration (t_{max}); steady state drug concentration (C_{ss}); and, elimination half life ($t_{1/2}$). Eleven subjects completed the study, with one subject withdrawing from the study due to lipothymia occurring just before first dose administration and recurring 30 minutes after the first dose.

Pharmacokinetic parameters are presented in Figure 2 and Table 3. C_{max} was reached after approximately 9 hours (477 ± 259 pg/mL) on day 1 and was multiplied by approximately two-fold on day 6. Moreover, it remained well below the known threshold susceptible to trigger systemic adverse events such as tachycardia and tremor, the latter reported as being approximately 3,000-3,500 pg/mL. Terbutaline steady state concentration was achieved after the first dose

(mean \pm SEM: 287 ± 96 pg/mL). The mean C_{ss} was 10 to 15 times less than therapeutic concentrations of terbutaline for intravenous preterm labor therapy described in the prior art. See Lyrenas, S, Grahnen A, Lindberg B. et al., *Pharmacokinetics of Terbutaline During Pregnancy*, *Eur. J. Clin. Pharmacol.*, 29:619-23 (1986). Comparison of the AUC_{0-24} for days 1 and 6 revealed a two-fold increase. Mean $t_{1/2}$ estimates were 51 hours on day 6.

TABLE 3: Multiple Dose Study, Pharmacokinetic Parameters

Multiple Dose Study			Pharmacokinetic Parameters (mean \pm SEM)				
Terbutaline Dose	Day	n	C_{max} (pg/mL)	T_{max} (h)	C_{ss} (pg/mL)	$t_{1/2}$ (h)	$AUC_{0 \text{ to } 48}$ (pg.h/mL)
0.4%	1	11	477 ± 259	9 ± 6	287 ± 96	---	6896 ± 2304
0.4%	6	11	769 ± 465	9 ± 5	563 ± 339	51 ± 91	13512 ± 8135

Example 3: A Dose Comparison

Both the single and multiple dose studies discussed in the preceding examples also evaluated the 0.8% w/w concentration. The average age \pm SD for the single and multiple dose studies at the 0.8 dose were 26 ± 3.42 and 26 ± 4.12 , respectively. The pharmacokinetic parameters from the study follow in Tables 4 and 5.

TABLE 4: Single Dose Study, Pharmacokinetic Parameters

Single Dose Study		Pharmacokinetic Parameters (mean \pm SEM)				
Terbutaline Dose	n	C _{max} (pg/mL)	T _{max} (h)	C _{ss} (pg/mL)	t _{1/2} (h)	AUC _{0 to 48} (pg.h/mL)
0.8%	8	787 \pm 434	10 \pm 3	579 \pm 300	20 \pm 7	23222 \pm 13530

TABLE 5: Multiple Dose Study, Pharmacokinetic Parameters

Multiple Dose Study			Pharmacokinetic Parameters (mean \pm SEM)				
Terbutaline Dose	Day	n	C _{max} (pg/mL)	T _{max} (h)	C _{ss} (pg/mL)	t _{1/2} (h)	AUC _{0 to 48} (pg.h/mL)
0.8%	1	10	794 \pm 394	11 \pm 5	567 \pm 322	---	13618 \pm 7718
0.8%	6	10	1537 \pm 906	9 \pm 2	1135 \pm 679	19 \pm 4	27246 \pm 16299

As can be seen in Figures 3 and 4, the serum terbutaline levels in both cases did not reach known levels for toxicity (3000 pg/ml), nor did they even therapeutic concentrations for other conditions such as asthma (1600 pg/ml). A number of patients in the study (40%), however, experienced side effects such as tachycardia at this dose. The occurrence of adverse events at this dose was an unexpected result of the invention, as again the serum levels did not reach known levels for toxicity. This dose can be a method of practicing the invention, but is certainly not the most preferred embodiment.

Example 4: Human Ex Vivo Uterine Perfusion Model

This model verifies the preferential direct delivery of terbutaline from the vagina to the uterus. In this study, uteri obtained from women undergoing hysterectomies for benign diseases were immediately connected to an organ

perfusion system in which temperature, CO₂ concentration, uterine artery pressure and flow were maintained constant. A perfusion model was opened without recirculation. The direct transfer of terbutaline from the vagina to the uterus was analyzed by applying a mixture of tritiated [³H] terbutaline and unlabeled
5 terbutaline to the cuff of vaginal tissue remaining attached to the cervix after the hysterectomy. Tritiated terbutaline was only used for autoradiography analysis of sections of uterine tissue. The experiments were interrupted at predetermined time intervals after vaginal applications (3 to 12 hours). At the end of the perfusion period, ³H and ¹⁴C radioactivity was measured in endometrial and
10 myometrial samples. Tritiated water and ¹⁴C dextran helped to determine that the extend of non-specific vagina to uterus transport (due to leaks of the system) was less than 10%. The myometrial extraction of terbutaline and its corresponding venous outflow during the 12 hour uterine perfusions are shown in Figure 3 below. The ³H terbutaline started to be recovered in the venous effluent uterine during the
15 first 3 hours.

Terbutaline flow was maximal at the 6th-9th hour and then decreased for up to 48 hours of perfusion. Terbutaline flow in the venous effluent uterine is the reflection of terbutaline exiting from the organ. Accumulation of tritiated terbutaline was maximal in the myometrium at 12 hours of perfusion. (Mean \pm SD of $18.40 \pm$
20 3.40 ng/100 mg of tissue) and decreased slowly. Significant accumulation of ³H terbutaline still remained at 48 hours of perfusion, with 20% of the original concentration present.

These data demonstrate that a *FIRST UTERINE PASS EFFECT*[®] also occurs when terbutaline is delivered vaginally. The nature of the active ingredient
25 and the utilized bioadhesive delivery system of the present invention seem even to be responsible for a more delayed and prolonged delivery of vaginal terbutaline gel than the one described for vaginal progesterone. Indeed, it is unexpected that the maximal myometrial concentration of terbutaline occurred later than that for progesterone. Further, it is notable that terbutaline in the myometrium was shown
30 to last over 48 hours after a single vaginal application. Vaginal terbutaline gel achieves high myometrial concentrations of terbutaline relative to its low systemic

concentrations and, consequently, to maximizes utero relaxant effects and minimizes systemic adverse effects.

Any and all publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein
5 incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Reasonable variations, such as those which would occur to a skilled
10 artisan, can be made herein without departing from the spirit and scope of the invention.

WE CLAIM:

1. A pharmaceutical composition comprising a therapeutically effective amount of a β -adrenergic agonist together with a pharmaceutically acceptable bioadhesive carrier.
2. The composition of claim 1 wherein the β -adrenergic agonist is terbutaline.
3. The composition of claim 2 wherein the bioadhesive carrier comprises a cross-linked carboxylic polymer.
4. The composition of claim 3, wherein the concentration of terbutaline is from 0.1 to 0.4% weight/weight.
5. The composition of claim 4, wherein the polymer is polycarbophil.
6. The composition of claim 5, wherein the β -adrenergic agonist is terbutaline and the composition is prepared so that a dosage of about 1 to 1.5 g of composition delivers from about 1 to 4 mg of terbutaline.
7. A method of preventing or treating dysmenorrhea comprising administering vaginally to a host in need thereof the pharmaceutical composition of claim 1.
8. The method of claim 7, wherein the β -adrenergic agonist is terbutaline and the dosage of composition administered contains from 1 to 4 mg of terbutaline.
9. The method of claim 7, wherein the composition is administered every 12 to 48 hours during dysmenorrhea.

10. The method of claim 7, wherein the composition is administered every 24 hours during dysmenorrhea.
11. A method of preventing or treating premature labor comprising administering the composition of claim 1 vaginally, in a therapeutically effective amount.
12. The method of claim 11, wherein the β -adrenergic agonist is terbutaline and the dosage of composition administered contains from 1 to 4 mg of terbutaline.
13. The method of claim 11, wherein the composition is administered every 12 to 48 hours to prevent or treat premature labor.
14. The method of claim 11, wherein the composition is administered every 24 hours to prevent or treat premature labor.
15. A pharmaceutical composition for vaginal administration of a treating agent to achieve local efficacy without detrimental blood levels of the treating agent, comprising a therapeutically effective amount of a treating agent together with polycarbophil.
16. A method of vaginally administering the composition of claim 15, in a therapeutically effective amount.
17. A pharmaceutical composition for vaginal administration of a treating agent during menses, comprising polycarbophil and a therapeutically effective amount of a treating agent.
18. Use of a β -adrenergic agonist together with a bioadhesive cross-linked carboxylic polymer carrier for the preparation of a pharmaceutical composition for the prevention or treatment of dysmenorrhea or premature labor.

19. The use according to claim 18, wherein the β -adrenergic agonist is terbutaline.
20. The use according to claim 19, wherein the cross-linked carboxylic polymer is polycarbophil.
21. The use according to claim 19, wherein a dosage of the composition contains from 1 to 4 mg of terbutaline.
22. Use of a treating agent together with a bioadhesive cross-linked carboxylic polymer carrier for the preparation of a pharmaceutical vaginal composition for effective local treatment without detrimental blood levels.

COL 2301 FR 01

SINGLE DOSE TERBUTALINE 1-2-4 mg

Mean \pm SEM

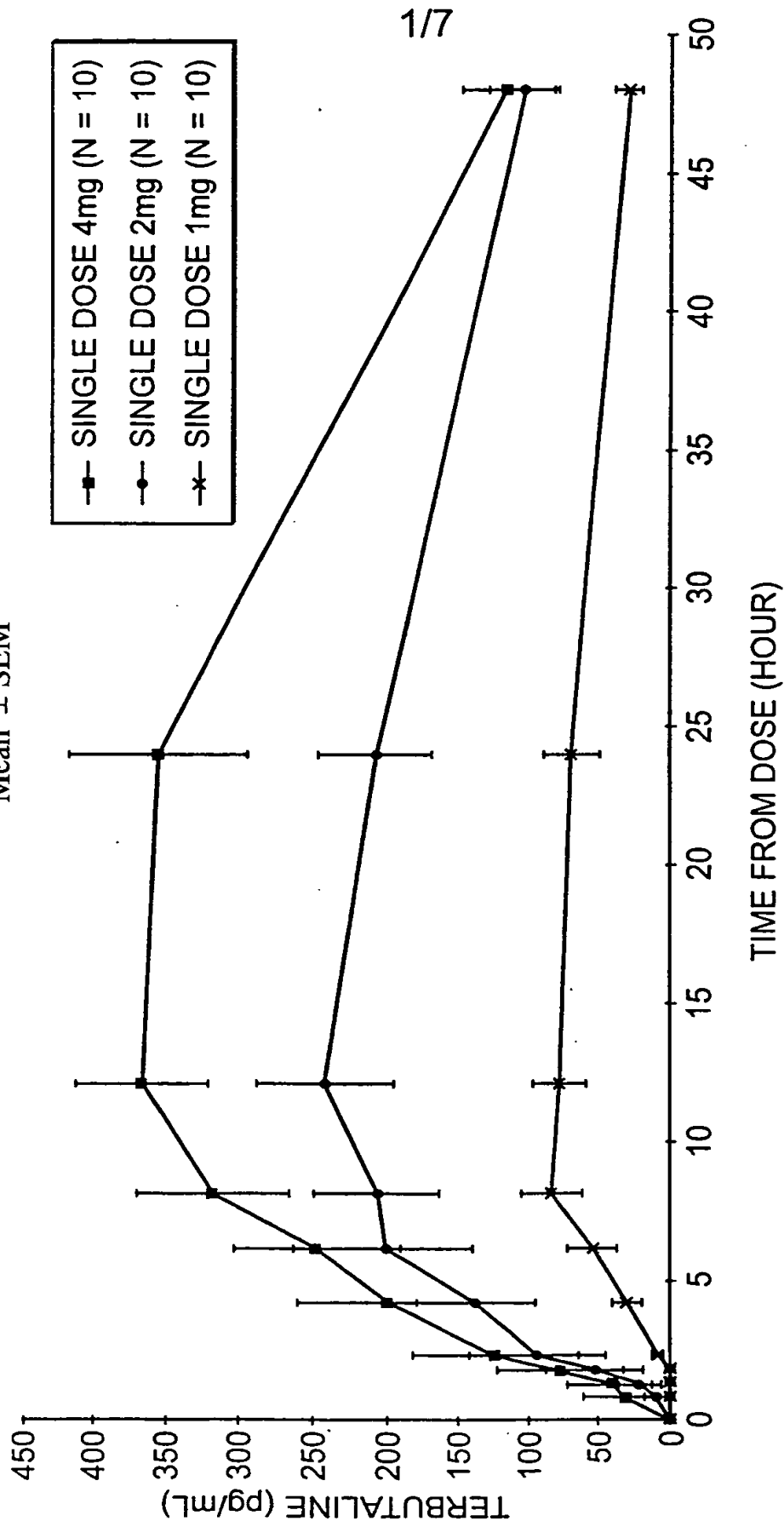


FIG. 1

STUDY COL 2301 FR 01

MULTIPLE DOSE TERBUTALINE 4 mg

SERUM TERBUTALINE CONCENTRATIONS
Mean \pm SEM (N = 11)

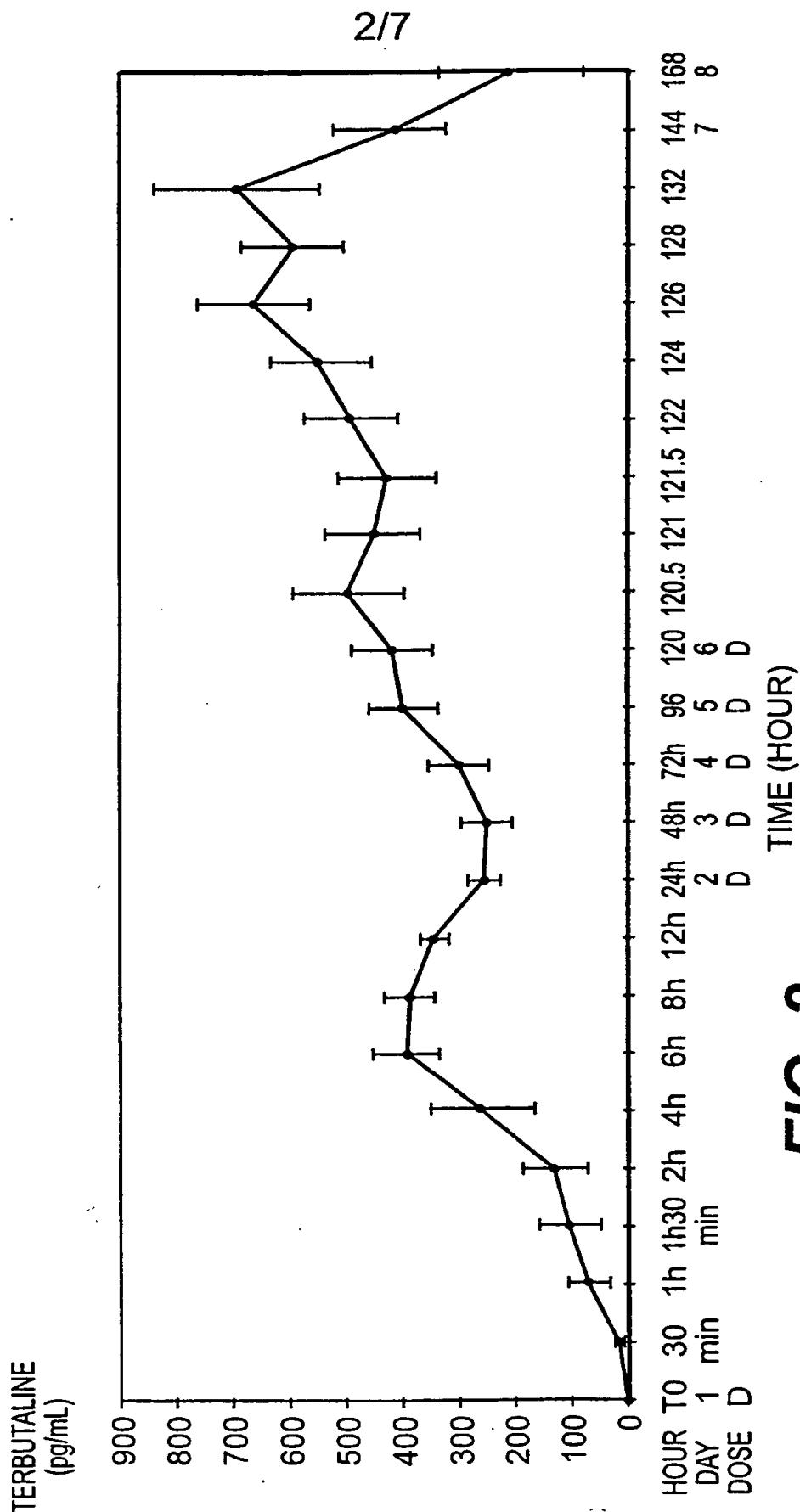


FIG. 2

STUDY COL 2301 FR 02
 MULTIPLE DOSE TERBUTALINE 8 mg
 SERUM TERBUTALINE CONCENTRATIONS
 Mean \pm SEM
 (N = 10)

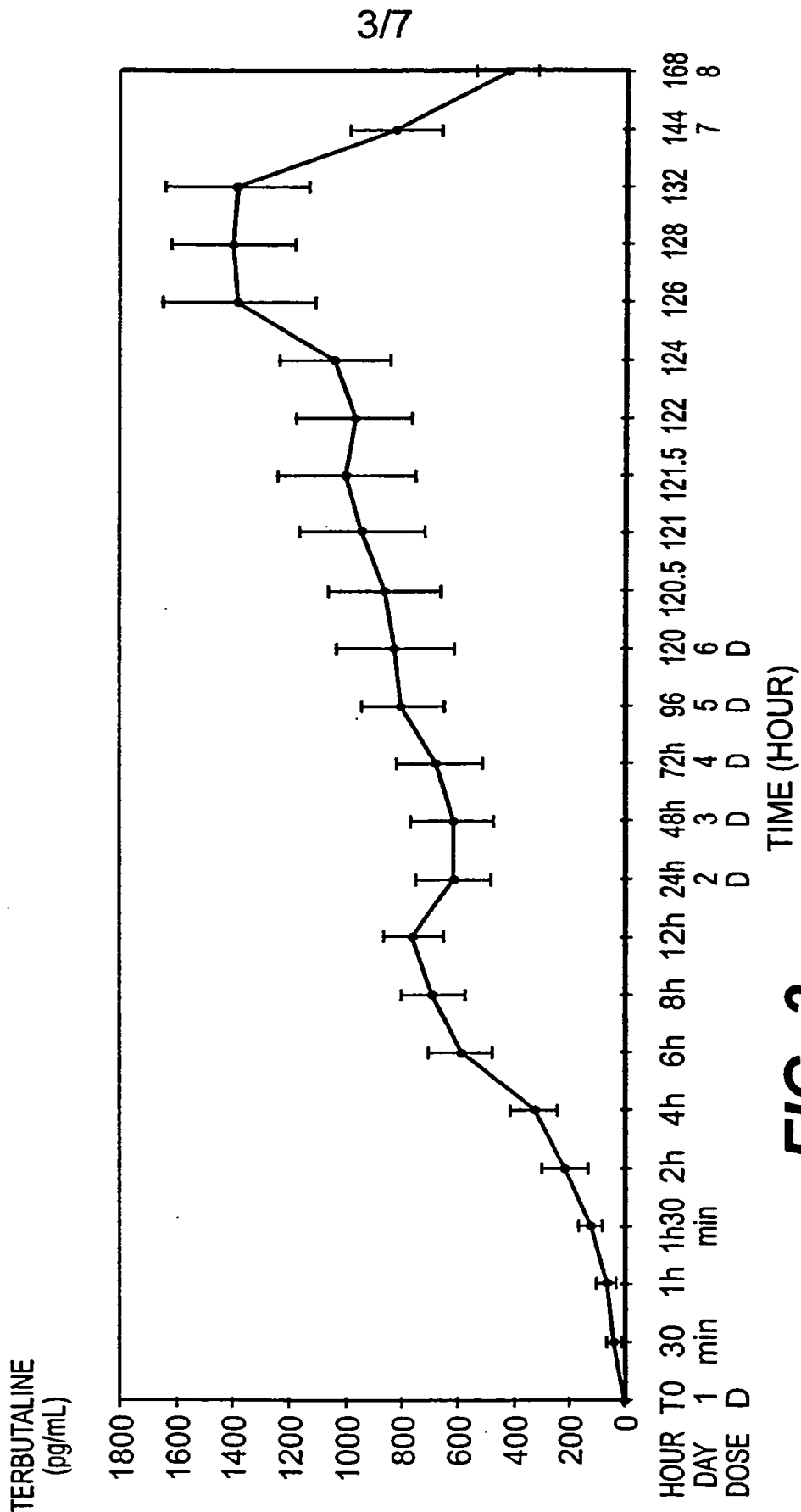


FIG. 3

STUDY COL 2301 FR 02

SERUM TERBUTALINE CONCENTRATIONS

Mean \pm SEM (N = 8)

TERBUTALINE (pg/mL)

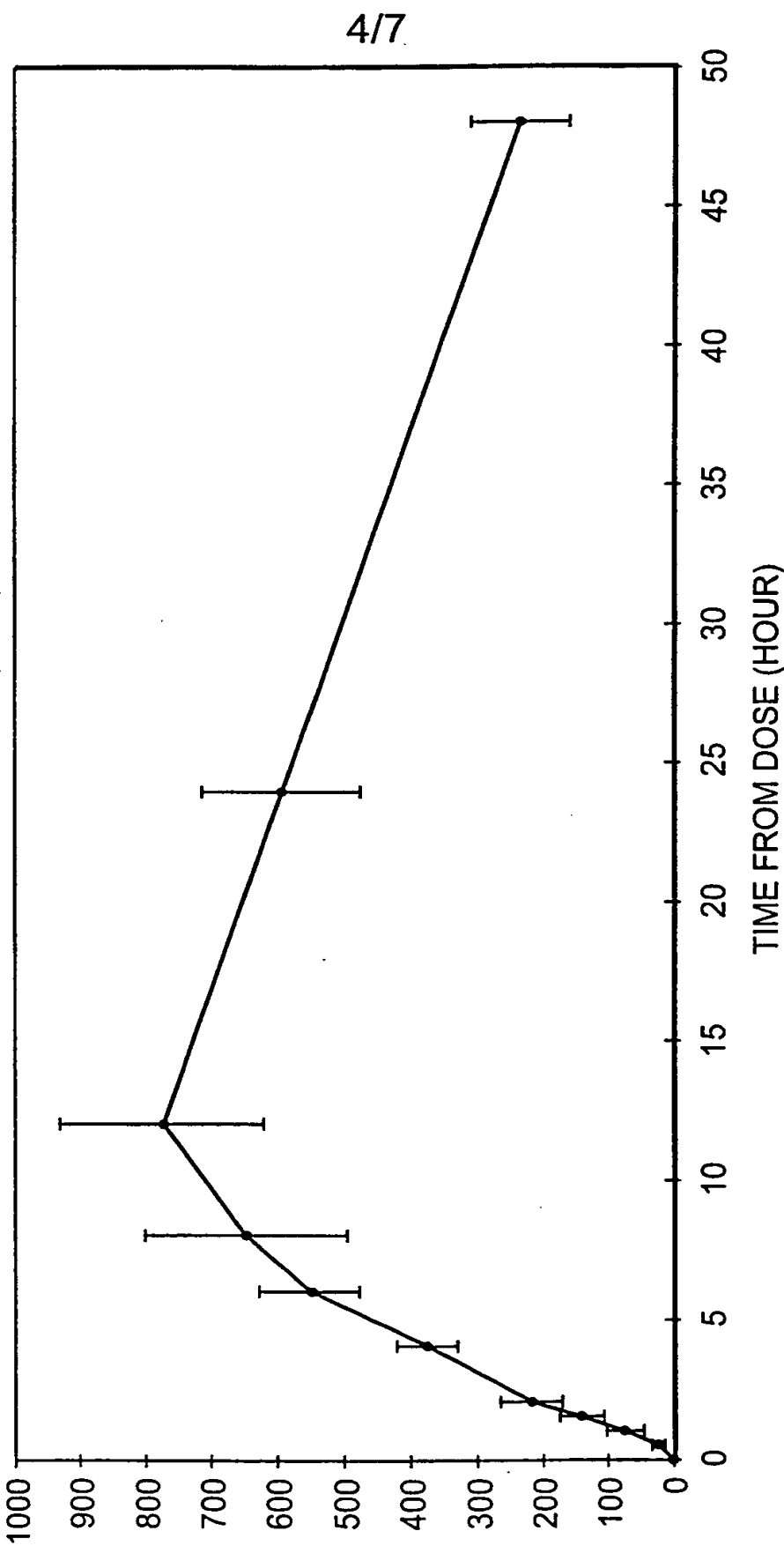


FIG. 4

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SINGLE DOSE STUDY MEAN HEART RATE

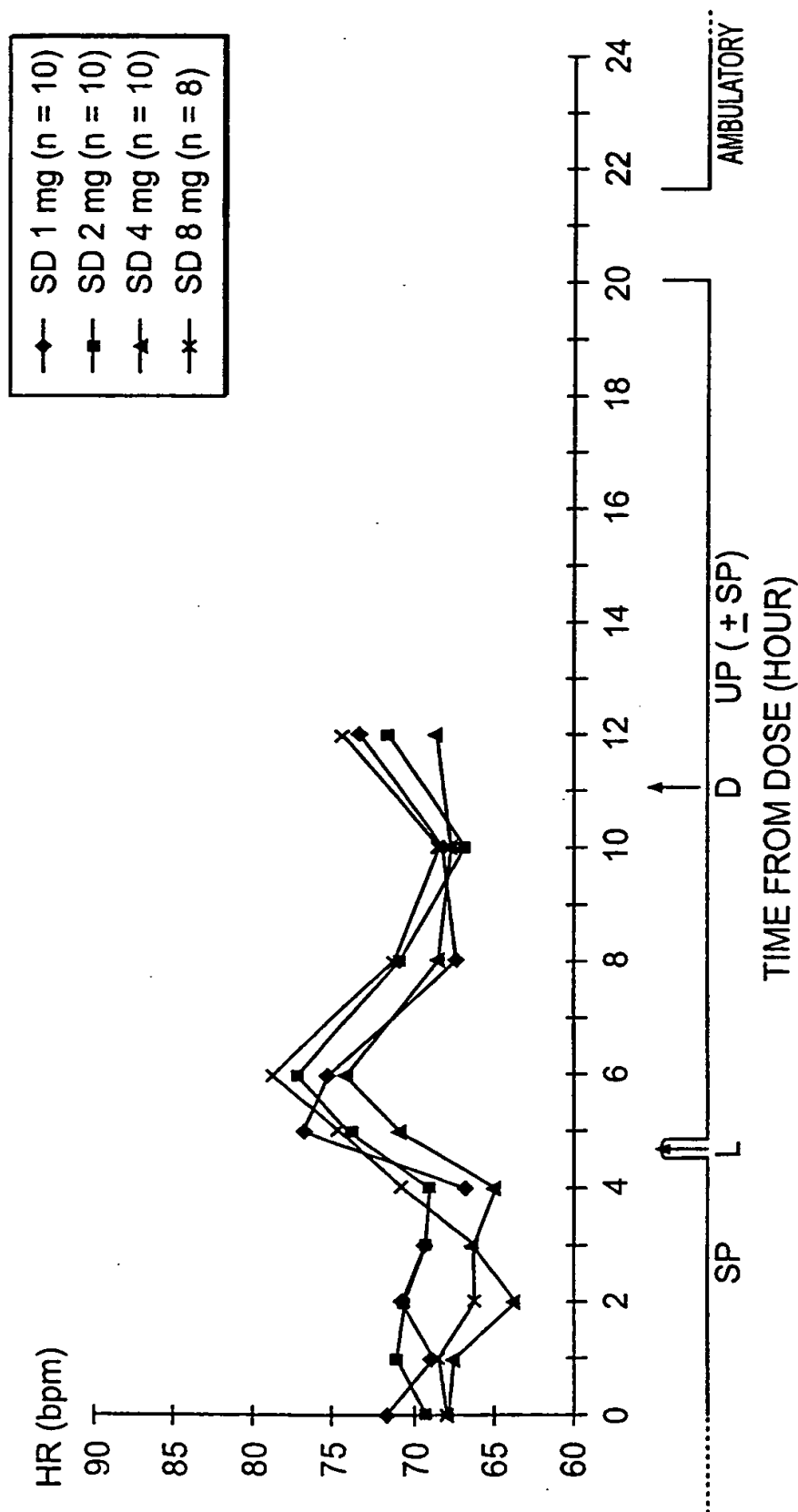


FIG. 5

SP: SUPINE POSITION L: LUNCH
UP: UPRIGHT POSITION D: DINNER

MULTIPLE DOSE STUDY MEAN HEART RATE

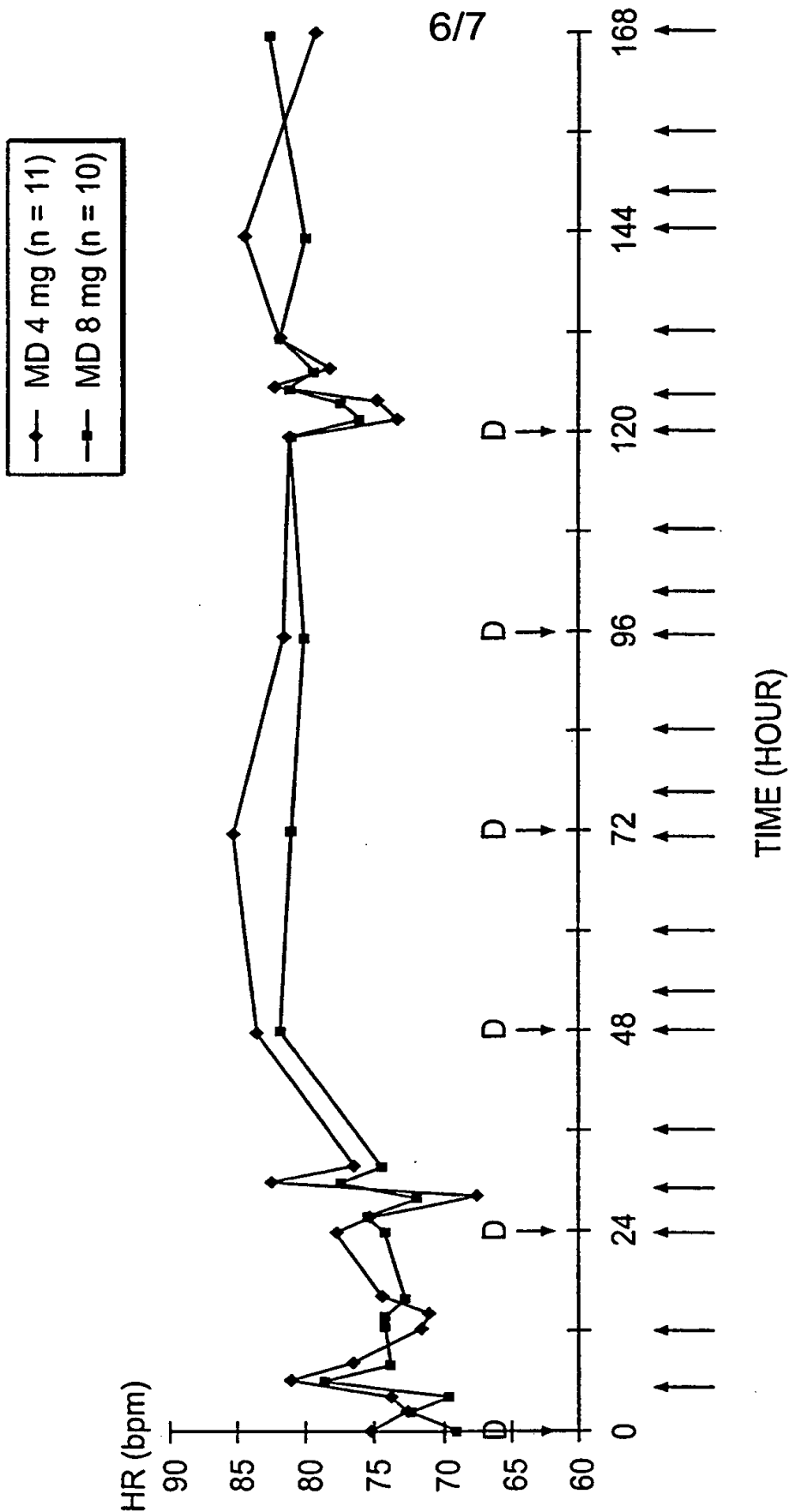


FIG. 6

D: TERBUTALINE ADMINISTRATION

↑: MEAL

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MYOMETRIAL TERBUTALINE INFLUX
MEAN \pm SD

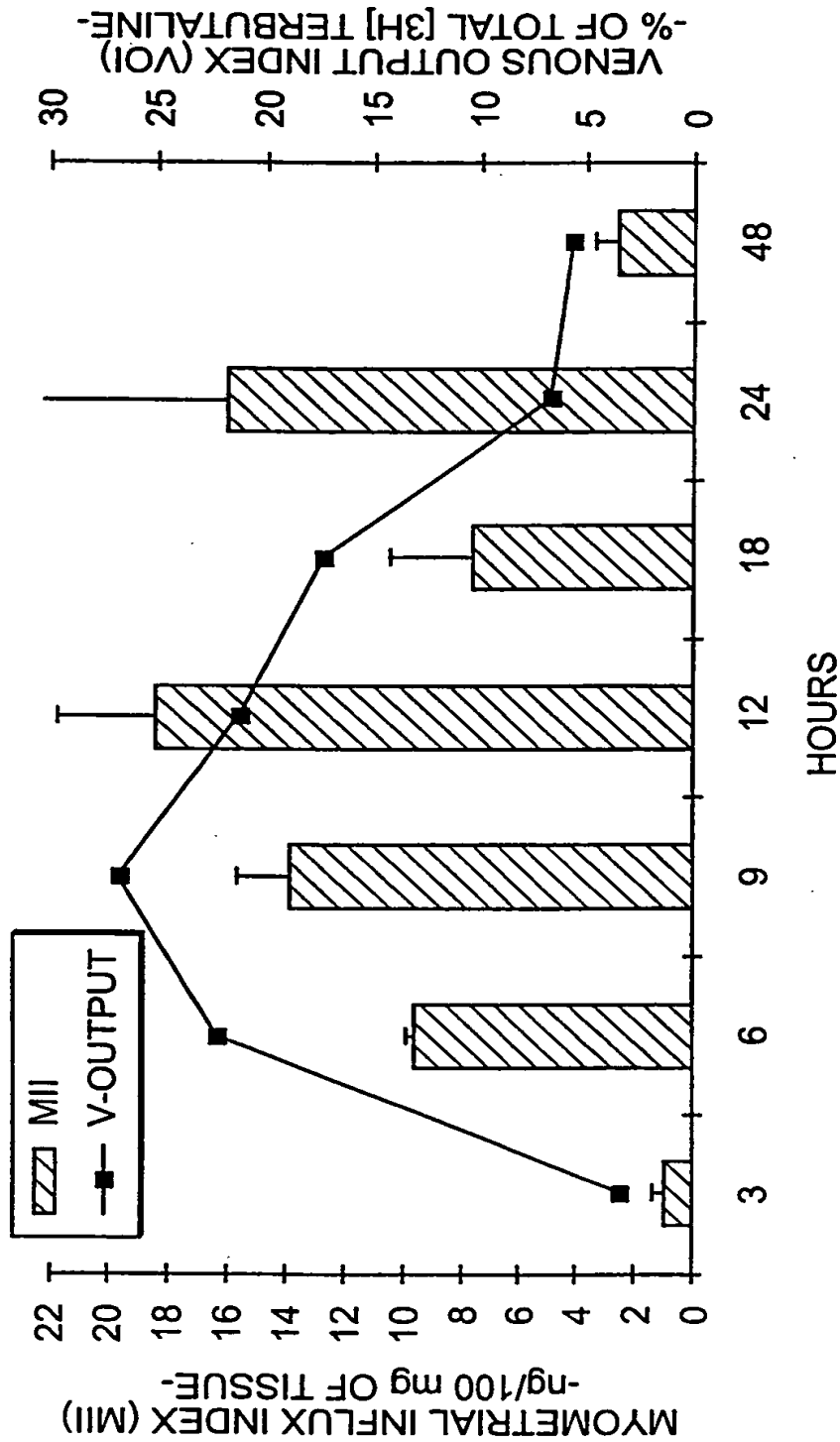


FIG. 7

SINGLE DOSE TERBUTALINE 1-2-4 mg

SERUM TERBUTALINE CONCENTRATIONS

Mean \pm SEM

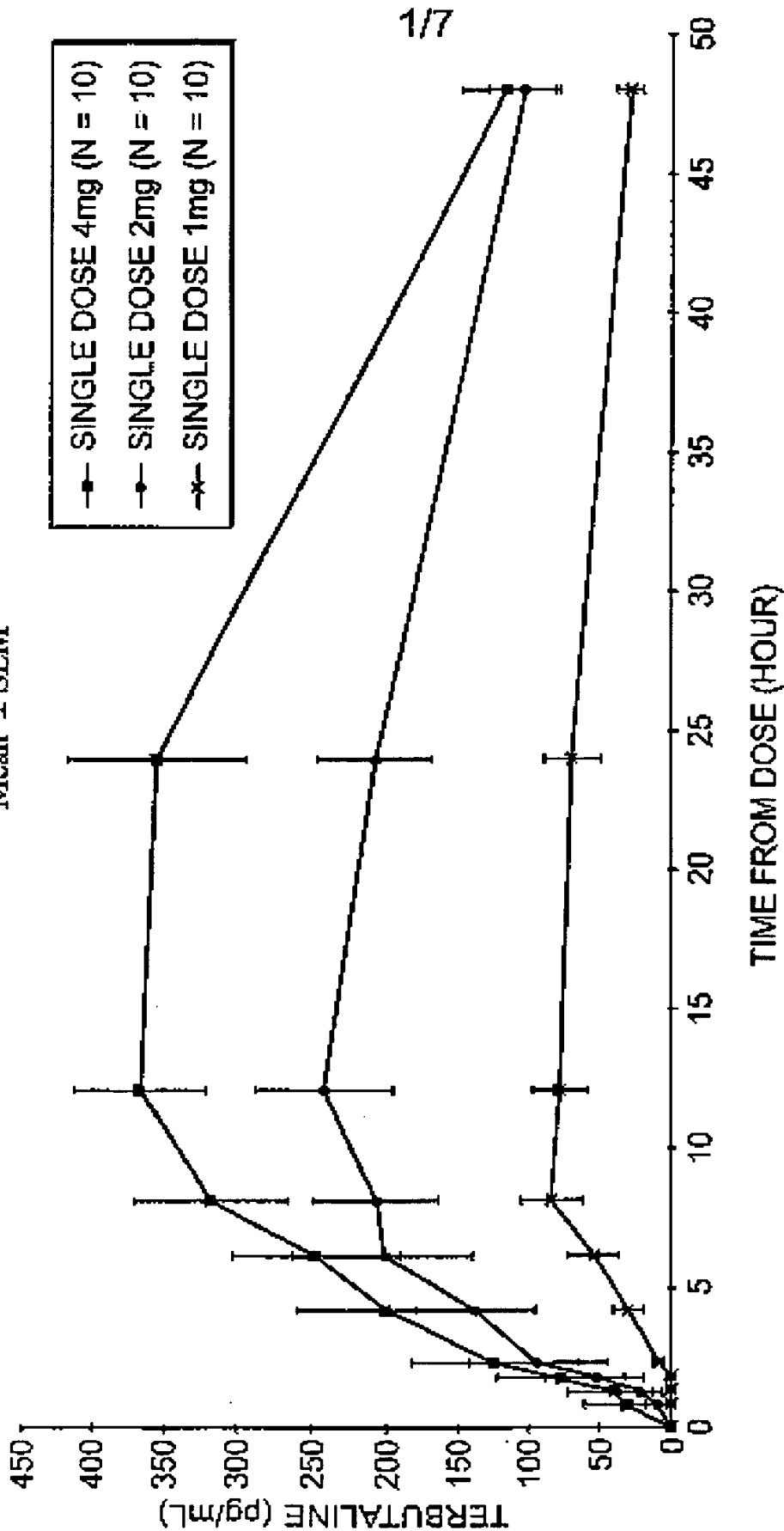


FIG. 1

STUDY COL 2301 FR 01

MULTIPLE DOSE TERBUTALINE 4 mg

SERUM TERBUTALINE CONCENTRATIONS
Mean \pm SEM (N = 11)

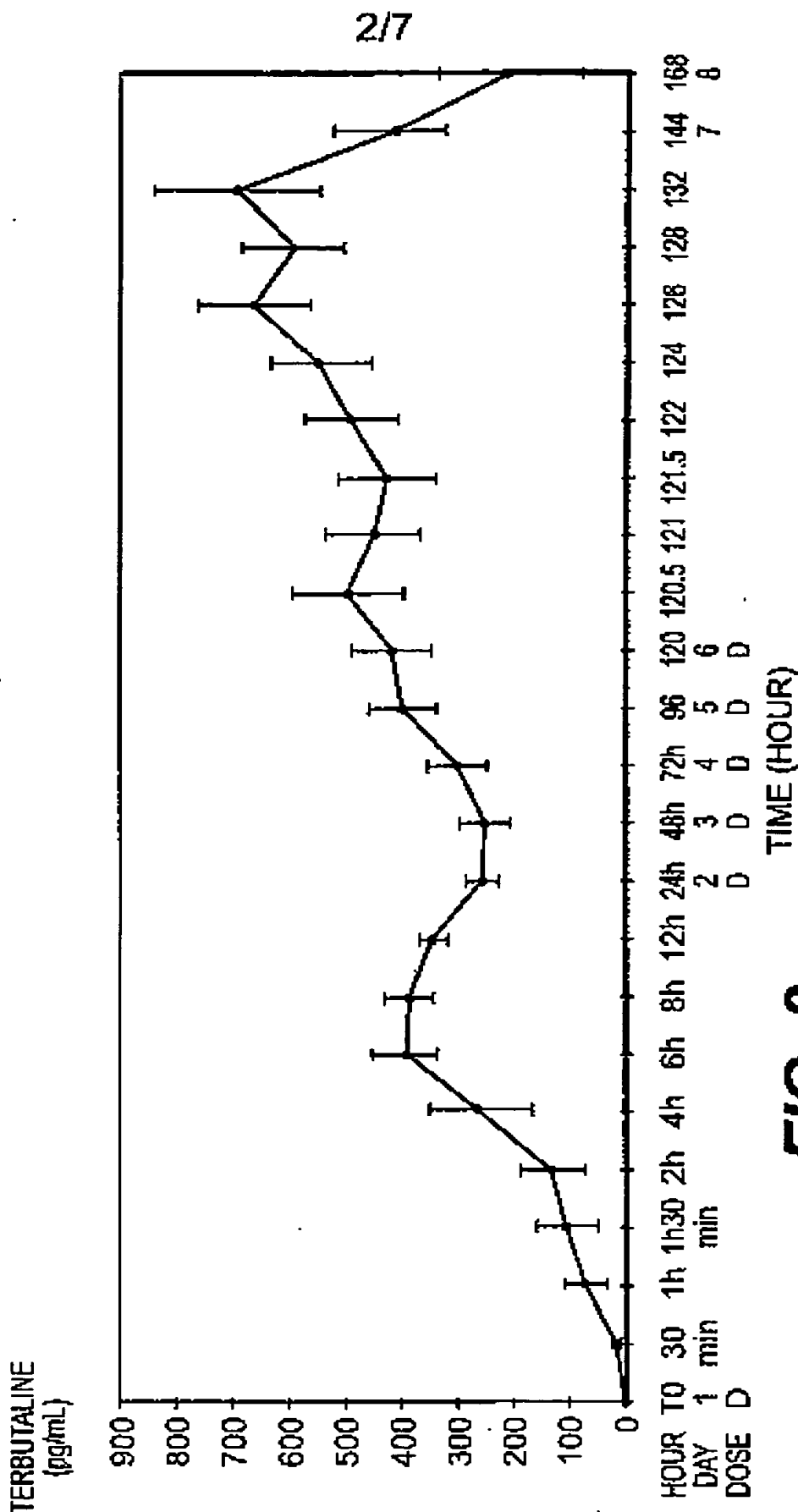


FIG. 2

STUDY COL 2301 FR 02
MULTIPLE DOSE TERBUTALINE 8 mg
SERUM TERBUTALINE CONCENTRATIONS
(N = 10)
Mean \pm SEM

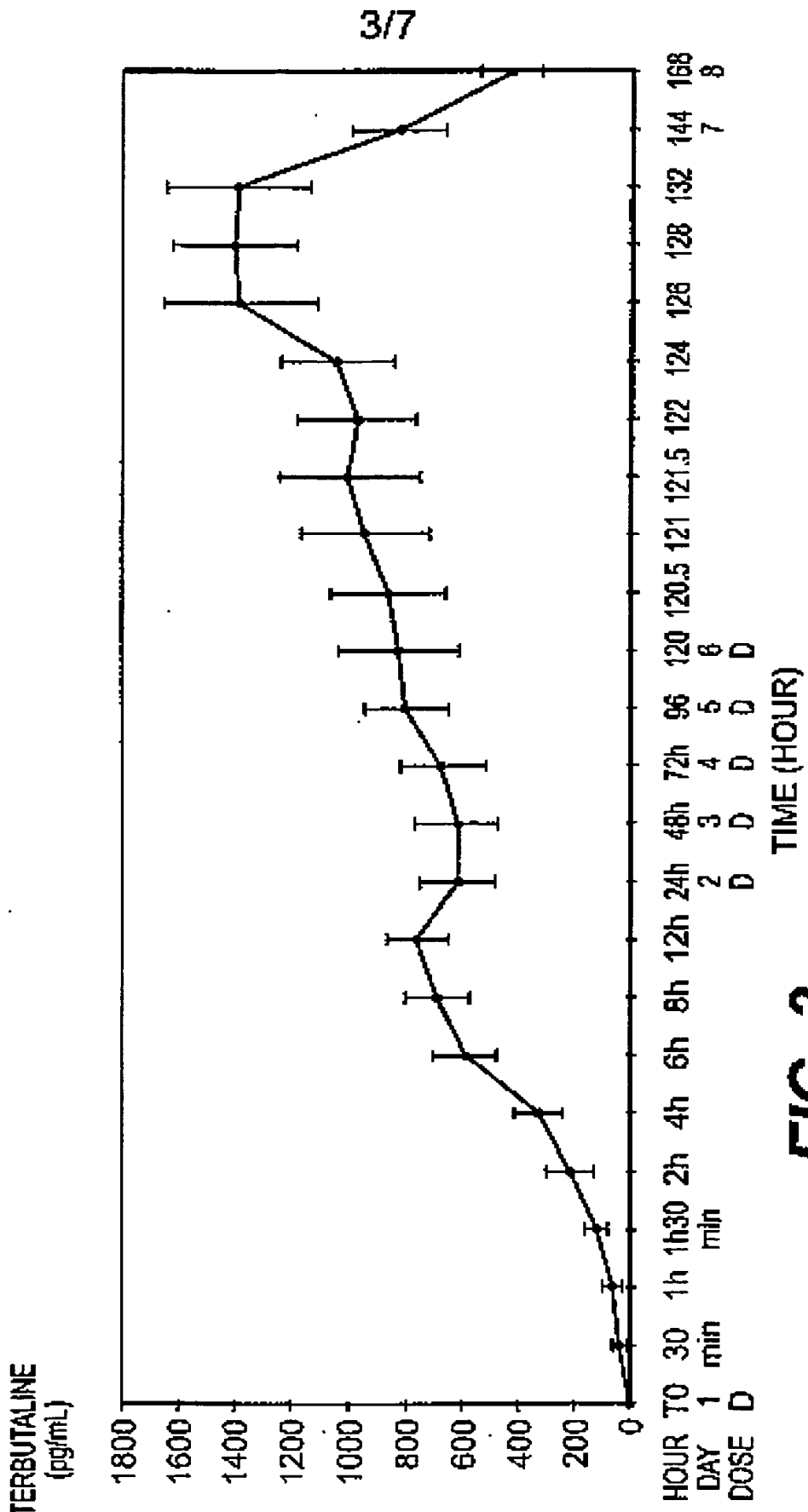


FIG. 3

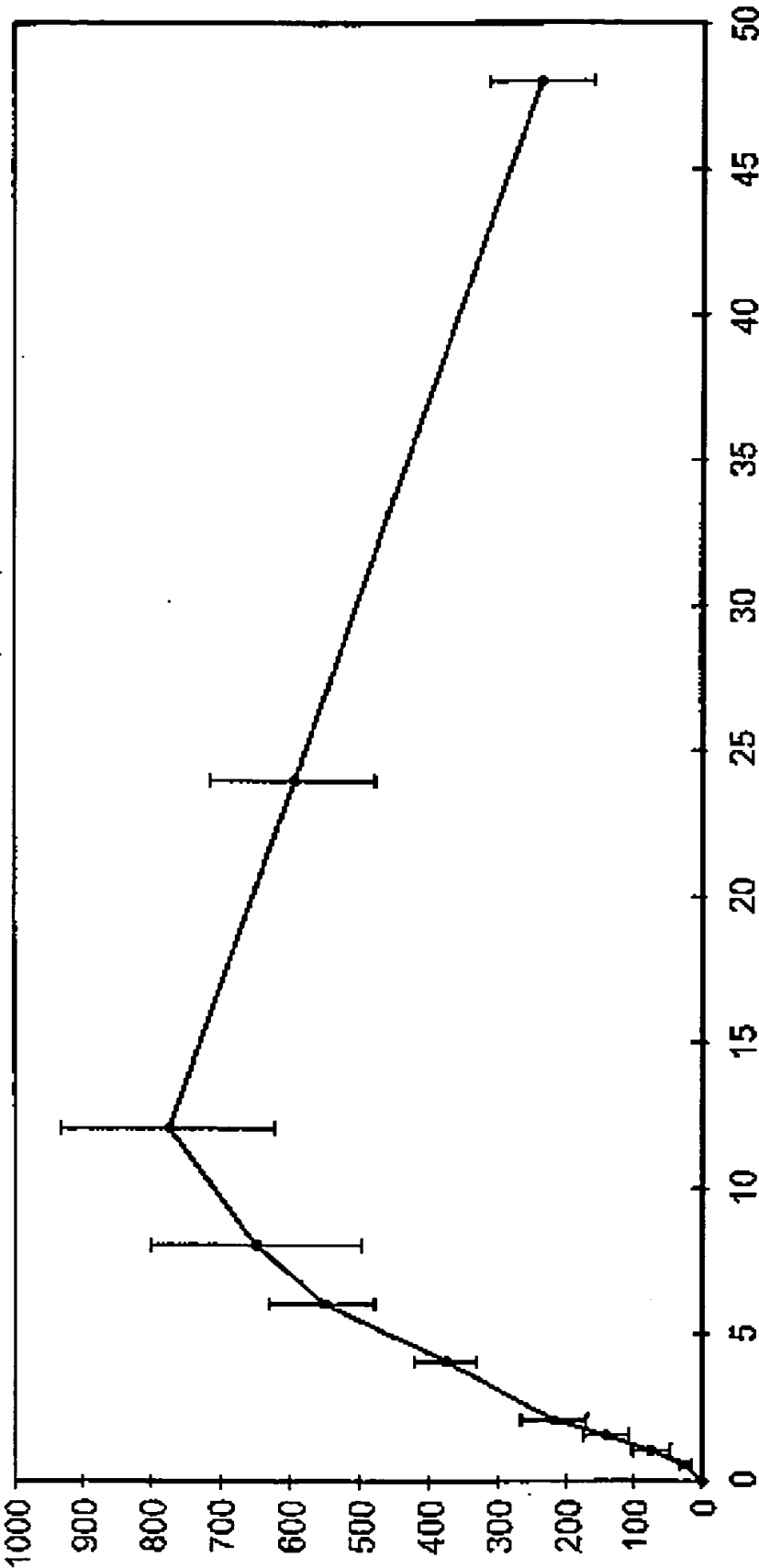
STUDY COL 2301 FR 02

MULTIPLE DOSE TERBUTALINE 8 mg

SERUM TERBUTALINE CONCENTRATIONS

Mean \pm SEM (N = 8)

TERBUTALINE
(pg/mL)



TIME FROM DOSE (HOUR)

FIG. 4

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SINGLE DOSE STUDY MEAN HEART RATE

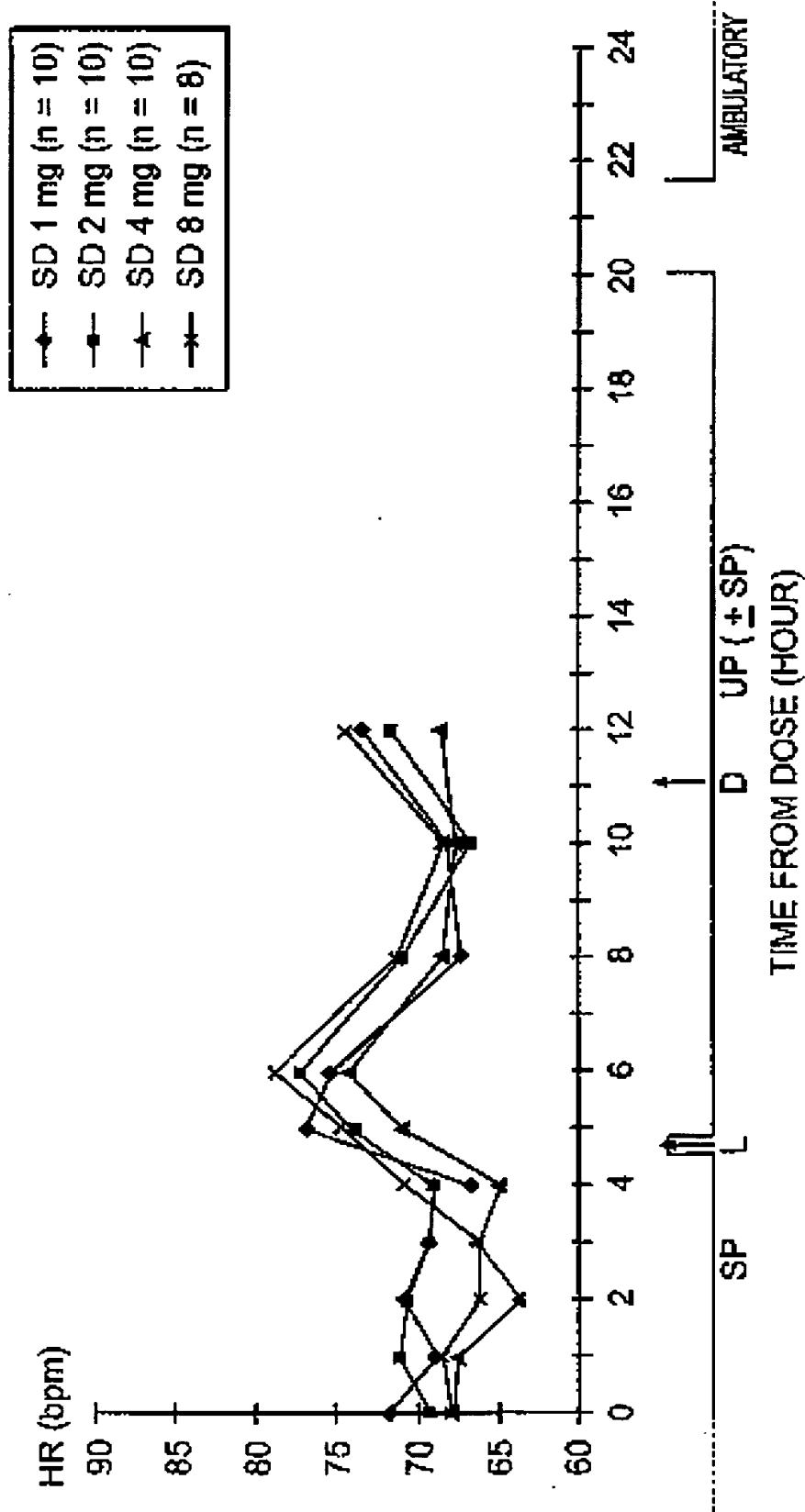
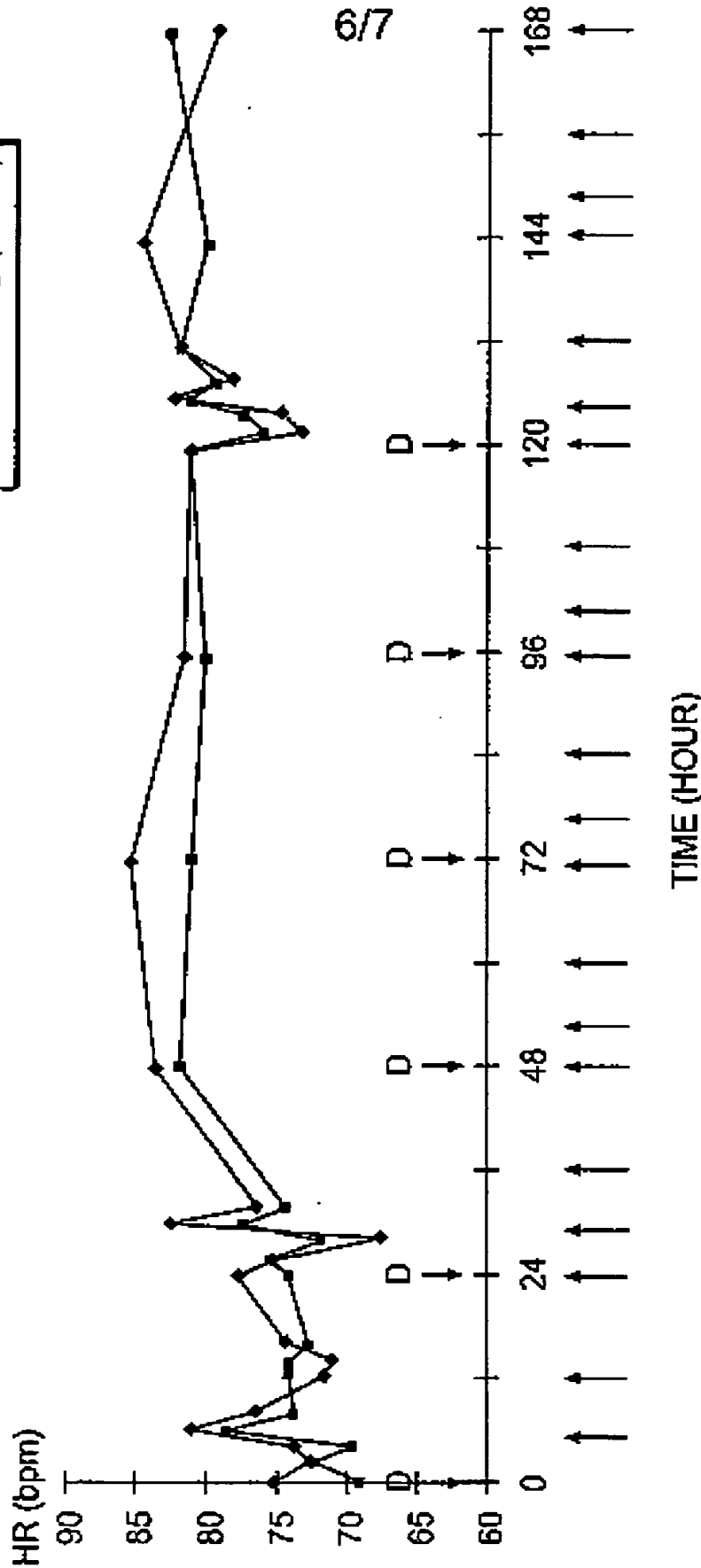
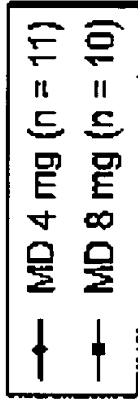


FIG. 5

SP: SUPINE POSITION L: LUNCH
UP: UPRIGHT POSITION D: DINNER

MULTIPLE DOSE STUDY MEAN HEART RATE



TIME (HOUR)

FIG. 6

D: TERBUTALINE ADMINISTRATION

↑: MEAL

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MYOMETRIAL TERBUTALINE INFUX
MEAN \pm SD

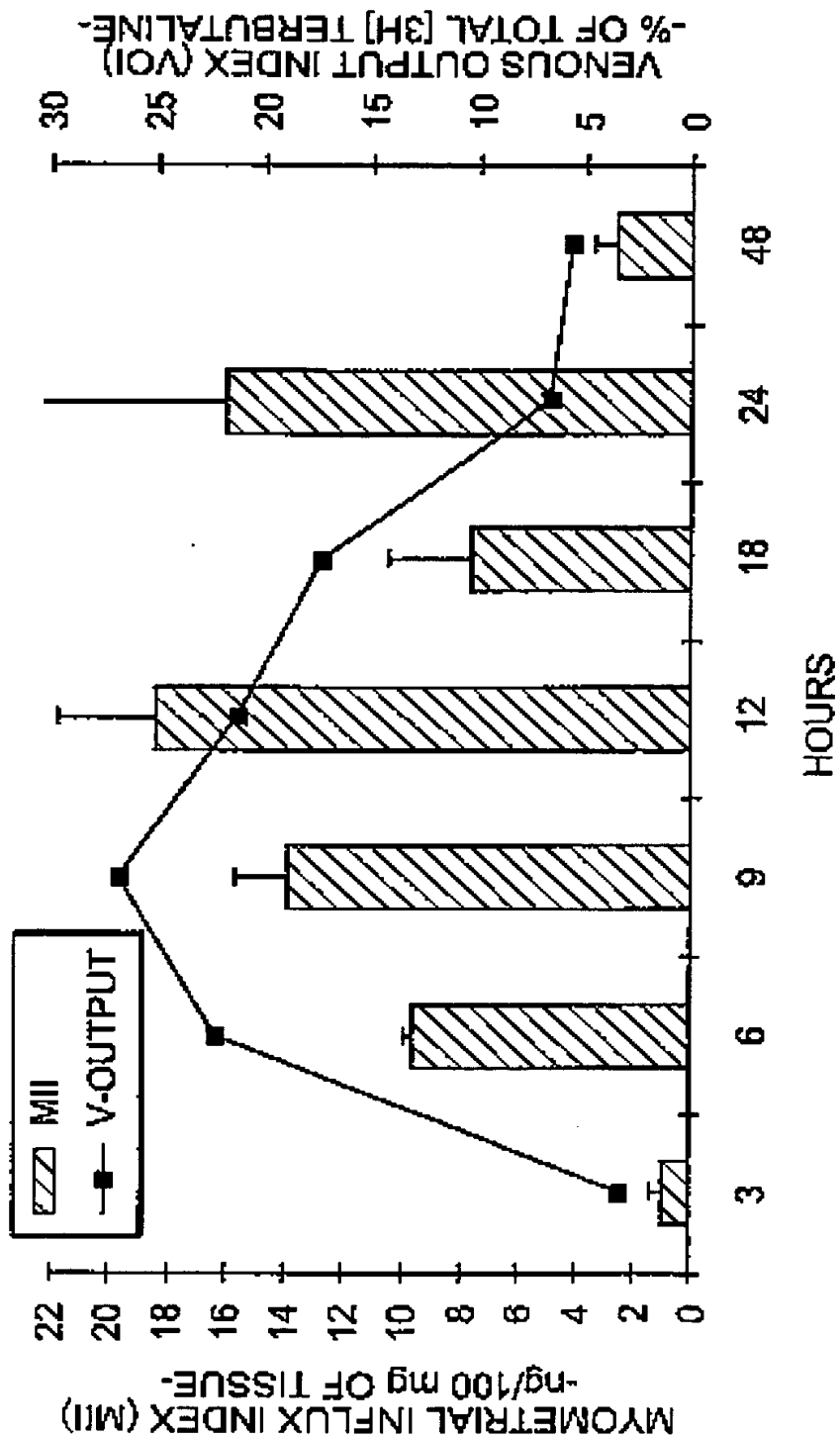


FIG. 7



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(88) Date of publication of the international search report: 14 May 1999 (14.05.99)			
(54) Title: A PHARMACEUTICAL COMPOSITION FOR TREATING DYSMENORRHEA AND PREMATURE LABOR			
(57) Abstract <p>The present invention teaches a composition comprising a β-adrenergic agonist in a bioadhesive carrier. Preferably, the composition comprises terbutaline in polycarbophil. The present invention additionally teaches the local administration of a β-adrenergic agonist for the purpose of treating or preventing dysmenorrhea or premature labor. Using this composition and the method of treatment provides sufficient local levels of the drug to provide therapeutic efficacy, but avoids many untoward adverse events.</p>			

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/18538

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/00 A61K47/32 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 56323 A (UMD INC., U.S.A.) 17 December 1998 see the whole document ---	1-24
X, P	WO 98 23292 A (MONSANTO) 4 June 1998 see claims 1, 8, 13, 14, 19, 20, 31, 32 ---	1, 2
Y	FR 2 720 276 A (C. BOYER-B. GALICHON) 1 December 1995 see claims 1, 3, 6, 7, 9 see page 4, line 29 - line 34 see page 5, line 26 - line 29 ---	1-24
Y	WO 93 00058 A (NOVEN) 7 January 1993 see claims 1, 2, 10, 11, 16-18 see page 17, line 27 - page 18, line 22 --- -/--	1-24



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

17 March 1999

Date of mailing of the international search report

25/03/1999

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Scarponi, U

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/18538

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Week 8412 Derwent Publications Ltd., London, GB; AN 84-071329 '12! XP002096704 see abstract & JP 59 025320 A (WATANABE YAKUHI KOGYO KK) 9 February 1984 ---	1-24
A	EP 0 147 780 A (MERCK) 10 July 1985 see the whole document ---	1-24
A	WO 96 10989 A (W. BOLOGNA-H.L. LEVINE) 18 April 1996 cited in the application see the whole document ---	1-24
A	WO 95 07699 A (COLUMBIA LABS. INC., U.S.A.) 23 March 1995 cited in the application see the whole document -----	1-24

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/18538

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-14 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/18538

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